SYNTHESIS AND CHARACTERIZATION OF 6-*O*-α- AND 6-*O*-β-D-GLUCOPYRANOSYLMORPHINE AND 6-*O*-β-D-GLUCOPYRANOSYL-CODEINE

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Abstract— 6-*O*-α- and β-D-glucopyranosylmorphine and 6-*O*-β-D-glucopyranosylcodeine have been prepared by condensations of 2,3,4,6-tetra-*O*-acyl-α-D-glucopyranosyl bromides with 3-*O*-acetylmorphine and codeine, respectively, followed by deprotection. Depending upon the method of condensation, variable amounts of orthoesters were found among the final products of condensation together with the desired glycosides. Highest yields of glycosides were obtained when 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide was the glycosyl donor, and when the condensation was promoted with silver triflate in the presence of a less than stoichiometric amount of 2,4,6-trimethylpyridine as the acid scavenger.

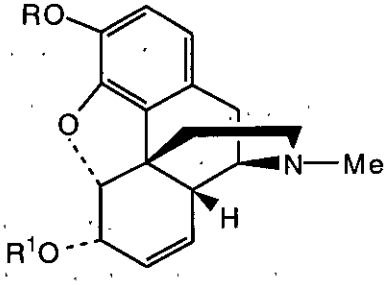
INTRODUCTION

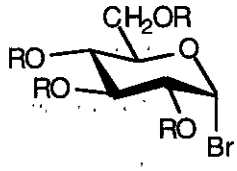
While the syntheses of 6-*O*-(β-D-glucopyranosyuronic acid)codeine and 6-*O*-(β-D-glucopyranosyluronic acid)morphine [codeine-6-yl and morphine-6-yl β-D-glucuronide, respectively] have been reported,[1] 6-*O*-β-D-glucopyranosylmorphine (morphine-6-yl β-D-glucopyranoside) (**8**) was previously described only in the form of a hydrochloride.[2] That preparation, as well as the preparation of 6-*O*-β-D-glucopyranosylcodeine (codeine-6-yl β-D-glucopyranoside) (**11**),[3] was carried out prior to the development of either chromatography or nmr spectroscopy and, thus, the compounds lack characterization in that regard. The 6-*O*-α-D-glucopyranosylmorphine (morphine-6-yl α-D-glucopyranoside) (**16**) has not been described. In order to rectify

this situation, we undertook the syntheses described herein as part of our structure-activity studies within the opioid series.

RESULTS AND DISCUSSION

In initial experiments, 3-*O*-acetylmorphine[4] (**2**) was treated with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**4**).[5] The reaction carried out in acetonitrile using mercuric cyanide[6] as the promoter was very slow. The glycosyl donor (**4**), which had been consumed after 3-4 days leaving most of the nucleophile unchanged, largely decomposed under these conditions (tlc). Two products, detected both by uv light and by charring with sulfuric acid, were isolated from the complicated reaction mixture by column chromatography in low yields as amorphous solids. Their chemical ionization mass spectra (cims) showed peaks at *m/z* 658 ($[M + H)]^+$) and 675 ([M + NH_4]), as expected for products of coupling of **2** with **4**.

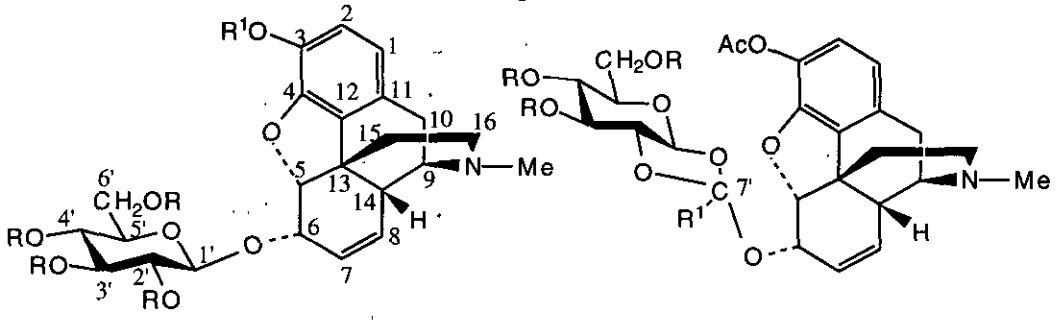




	R	R1		R
1	H	H	**4**	Ac
2	Ac	H	**5**	Bz
3	Me	H		

The proton nuclear magnetic resonance (^{1}H nmr) spectrum of the material having faster chromatographic mobility (major product) showed that the substance was the orthoester (**12**), a substance isomeric with the desired glycoside (**6**). In addition to signals characteristic of morphine, the ^{1}H nmr spectrum of the substance contained, *inter alia,* a doublet for H-1' at δ 5.84 ($J_{1,2}$ 5.4 Hz). One of the three methyl signals of the acetyl groups in the sugar moiety appeared upfield, at δ 1.76, which is a chemical shift characteristic of methyl groups of orthoacetates.[7] Compared to the ^{13}C nmr spectrum of morphine (**1**);[8] which shows only two signals in the range of δ 118-124, the spectrum of **8** shows, in that range, signals at δ 121.76, 121.33, and 119.08. The intensity of the signal at δ 121.33 was approximately half of each of those at δ 121.76 and 119.08. We have shown

previously,[9] in connection with analyses of the ^{13}C nmr spectra of related substances, that the low intensity signal at ~120 ppm represents the quaternary carbon of orthoesters (C-7', *cf.* accompanying formulas). That **12** was an orthoester was further confirmed when the substance was deacetylated to give **14**, the cims and ^1H nmr spectra of which were consistent with the anticipated structure.



	R	R^1		R	R^1
6	Ac	Ac	**12**	Ac	Me
7	Bz	Ac	**13**	Bz	Ph
8	H	H	**14**	H	Me
9	Bz	Me			
10	Ac	Me			
11	H	Me			

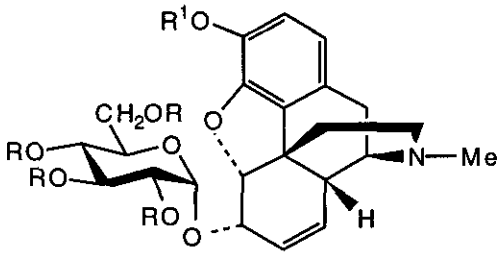
The minor product of the coupling of **2** and **4** was the desired β-glycoside (**6**), which was evident from the comparison of ^1H- and ^{13}C nmr spectra of the substance with those of **12**. Deacetylation of **6** with a catalytic amount of sodium methoxide in methanol yielded an amorphous substance, the ammonia cims of which contained peaks at *m/z* 448 ($[M + H]^+$ and 465 ($[M + NH_4]^+$), indicating structure (**8**). The structure was corroborated by its ^{13}C nmr spectrum, which could be confidently assigned by comparison with those of **1** and methyl β-D-glucopyranoside.[10] When condensation of the same synthons (**2**) and (**4**) was conducted under the standard conditions of glycosylation mediated by silver trifluoromethanesulfonate (triflate) in the presence of 2,4,6-trimethylpyridine as the acid scavenger, the nucleophile was converted to products of coupling more efficiently. Nevertheless, the ratio of the products (**6** and **12**) was approximately the same as of those formed in the reaction promoted with mercuric cyanide, *i.e.* the orthoester (**12**) was the major coupling product.

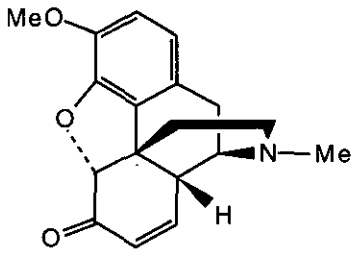
Garegg and Norberg[11] have observed that, during glycosylation reactions using acylated glycosyl donors, orthoesters were mainly formed in condensations where acetylated rather than benzoylated glycosyl donors were used in the presence of silver triflate and 2,4,6-trimethylpyridine. Therefore, in the next approach, 2,3,4,6-tetra-

O-benzoyl-α-D-glucopyranosyl bromide (**5**)[12] was used as the glucosyl donor. The reaction of **2** with **5** was conducted in the presence of an acid scavenger, to give products which were fractionated by column chromatography, and the three compounds isolated were identified by nmr spectroscopy as the orthoester (**13**), the α-glycoside (**15**), and the β-glycoside (**7**). Although the amount of orthoester (**13**) was substantial, the combined yield of glycosides (**7** and **15**) was now approximately equal to that of the orthoester. Accurate quantitation of these products was not possible because their clean-cut isolation from the complex reaction mixtures formed could not be achieved. Orthoesters have been suggested,[11] and also experimentally proven,[9,13] to be the intermediates and/or by-products in the formation of 1,2-*trans*-glycosides from 2-*O*-acylglycosyl halides. It has been suggested[12] that with some glycosyl acceptors the conjugate acid formed from the acid, liberated during the glycosylation reaction, and the acid acceptor may be, in certain cases, incapable of catalyzing complete rearrangement of the intermediate 1,2-orthoester to the 1,2-*trans*-glycoside. This appeared to be the case in the reaction involving **2** as the nucleophile. Therefore, the next reaction of **2** with **5** was conducted without an acid scavenger, notwithstanding that partial deblocking of ester protected functions could occur in the presence of triflic acid liberated during the condensation. In agreement with the findings of Garegg *et al.*[11] fewer by-products were formed under these conditions than those in the previous conversions conducted in the presence of an acid scavenger. Most notably, only a trace of **13** was present among the final products (tlc). Compounds (**15**) and (**7**) were isolated in a combined yield of 91%. Deacylation of **7** and **15** then readily gave **8** and **16**, respectively, in high yields, the latter of which was obtained crystalline. The ^{13}C nmr spectra of the substances were fully consistent with the anticipated structures. Compared to the chemical shift of C-6 of morphine, the spectra of **8** and **16** showed, as expected, the signal of the 6-*O*-glycosylated carbon atom shifted downfield. Lines in the ^{13}C nmr spectra of **8** and **16** reflecting, respectively, the presence of β- and α-D-glucosyl groups could be readily assigned with the aid of the spectra of the corresponding methyl glycosides.[9]

To obtain 6-*O*-β-D-glucopyranosylcodeine (**11**), we treated codeine (**3**) with glycosyl bromide (**5**) under the conditions which led successfully to the corresponding morphine derivative **7**. The resulting anomeric derivatives (**9**) and (**17**) and the minor by-products of the condensation have very similar chromatographic properties. Thus, separation of products of this coupling reaction was more difficult than that of the corresponding derivatives of morphine. While the β-anomer (**9**) was eventually obtained crystalline (67%), the α-isomer (**17**) could not be obtained in a pure state. The presence of **17** among the products was evident from nmr spectra of the material, obtained by chromatography of the crude product, present in the front of the zone containing products of condensation. The spectra showed the presence of a mixture of **9** and **17**. Deacylation of pure **9** gave amorphous

11, the ^{13}C nmr spectrum of which was fully supportive of the expected structure. The acetyl derivative (**10**) formed by acetylation of **11** was identical (tlc, nmr) with the compound previously reported.[3]





	R	R^1
15	Bz	Ac
16	H	H
17	Bz	Me
18	Ac	Me

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6-*O*-β-D-Glucopyranosylcodeine was previously obtained[3] by the condensation of **3** with **4** under the classical conditions of the Koenigs-Knorr reaction promoted by silver carbonate, followed by deacetylation of the intermediate, crystalline tetra-*O*-acetyl derivative (**10**). That procedure can no longer be thought suitable for the preparation of 6-*O*-glycoconjugates of codeine and related substances, due to the readily occurring, undesired oxidation of the allylic hydroxyl group of codeine under these conditions.[13] When we repeated the condensation of **3** with **4** exactly as described,[3] the reported yield of ~43% of **10** could not be reproduced. Monitoring the course of the reaction by tlc showed that a large part of the starting base (**3**) was converted to codeinone (**19**),[13] even before **4** was introduced into the reaction vessel. The extent of that conversion may depend on the quality of silver carbonate used as the condensation reagent. When the reaction was complete, tlc of the reaction mixture showed the presence of a large amount of the product of hydrolysis of **4**, a mixture of **10** and **18**, a large amount of **19**, and a small amount of unchanged **3**. Preparative chromatography then gave **10** and **19**.

In conclusion, 6-*O*-β-D-glucopyranosylmorphine (**8**), hitherto unknown in the free-base form, has been prepared. The correspnding, crystalline α-glycoside (**16**) is described for the first time. The original[3] synthesis of 6-*O*-β-D-glucopyranosylcodeineide (**11**) has been improved by using fully benzoylated, rather then acetylated[3] glucosyl donor as a one of the synthons, and by avoiding the use of silver carbonate as a promoter of the condensation reaction. The title compounds have been characterized by nmr spectroscopy.

EXPERIMENTAL

Optical rotations were measured at 25 °C with a Perkin-Elmer automatic polarimeter, Model 241 MC. Thin-layer chromatography (tlc) on precoated slides of Silica Gel G F_{254} (Analtech) was performed with *A*, 10:1 chloroform-methanol, *B*, 2:1.3:0.2 chloroform-methanol-25% aqueous ammonia, *C*, 15:1 chloroform-methanol, and *D*, 4.5:1 ethyl acetate-methanol. Detection was effected by charring with 5% sulfuric acid in ethanol and with uv light. Unless stated otherwise, preparative chromatography was performed using columns of Silica Gel 60 (Merck, No. 9385, or No. 15111), by gradient elution with solvent mixtures consisting of the same components as those used for tlc.

Nmr spectra were taken at 25 °C using Varian XL 300 spectrometer, and chemical shifts are reported relative to tetramethylsilane as the internal standard. The solvents of measurements are listed as required. Proton-signal assignments were aided by selective homonuclear decoupling. Signals in ^{13}C nmr spectra were assigned by comparison with assigned spectra of related substances[8,10] and, for certain compounds, the assignments were supported by DEPT experiments. Chemical ionization mass spectra (cims) were measured with a Finnigan 10151 D spectrometer. Electron impact mass spectra (eims) were measured at 70 eV using a VG 707 F spectrometer. Reactions requiring anhydrous conditions were performed under argon using common laboratory glassware, and reagents and solvents were handled with Hamilton, Series 1000 gas-tight syringes. Silver carbonate and silver triflate were purchased from Aldrich Chemical Company, and dried before use at 50 °C/133 Pa for 16 h. Other general methodologies were those previously described.[14]

6-*O*-α- (16) and β-D-Glucopyranosylmorphine (8). a) A mixture of **2** (0.31 g, 1 mmol), Drierite (1 g), and $Hg(CN)_2$ (190 mg, 0.75 mmol) in dry acetonitrile (5 ml) was stirred at room temperature for 1 h. The glycosyl donor (**4**) (616 mg, 1.5 mmol) was added, and the suspension was stirred with the exclusion of atmospheric moisture until tlc (solvent *A*) showed that **4** was no longer present (~3-4 days). A complicated reaction mixture resulted but two major products were detected by both charring with sulfuric acid and by uv light (tlc). The mixture was filtered, concentrated, and the solution of the residue in dichloromethane was washed with aqueous 1 M KBr solution. The organic phase was dried, concentrated, and the residue was chromatographed. Orthoacetyl derivative (**12**); amorphous, cims, *m/z* 658 ($[M + 1]^+$), and 675 ($[M + 18]^+$); ^1H nmr ($CDCl_3$) δ 5.84 (d, $J_{1,2}$ 5.4 Hz, H-1), 2.46 (N-CH_3), 2.25 (3-O-$COCH_3$), 2.14, 2.09 (3- and 6-proton singlets, 3 x $COCH_3$, D-glucose moiety), 1.76 (orthoacetyl CH_3); ^{13}C nmr ($CDCl_3$) δ 121.33 (C-7') and 97.31 (C-1').

β-Glycoside (**6**); amorphous, cims, *m/z* 658 ([M + 1]$^+$), and 675 ([M + 18]$^+$); ^{1}H nmr ($CDCl_3$): δ 2.02, 2.03, 2.07, 2.10, 2.31, and 2.46 (6 x $COCH_3$; ^{13}C nmr ($CDCl_3$): δ 99.81 (C-1'); the signal of the quaternary orthoester carbon atom was not present. An intermediate, mixed fraction was also obtained.

A solution of **6** (~60 mg) in methanol (5 ml) was made strongly alkaline by addition of methanolic 1 M sodium methoxide. The solution was kept at room temperature for 3 h, and then neutralized with Amberlite IR 120 (H$^+$-form) resin avoiding a large excess of the resin, and the crude product was chromatographed (solvent *B*), to give **8** as an amorphous, water soluble, hygroscopic solid (30 mg, 75%): $[\alpha]_D$ -132° (c 1, water); cims, *m/z* 448 ([M + 1]$^+$), 465 ([M + NH_4]$^+$), 198 ([M - morphine + NH_4]$^+$); ^{1}H nmr (CD_3OD-D_2O) δ 4.77 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1'), 3.92 (bd, 1 H, H-6'a), 3.73 (dd, 1H, $J_{5',6'b}$ 5.8 Hz, $J_{6'a,6'b}$ 12.2 Hz, H-6'b), and signals for the protons of the morphine moiety; ^{13}C nmr (CD_3OD) δ 147.26 (C-4), 139.87 (C-3), 132.13 (C-7), 131.51 (C-12), 129.12 (C-8), 126.41 (C-11), 120.45 (C-1), 117.76 (C-2), 102.86 (C-1'), 90.07 (C-5), 77.92, 77.76, 75.29, 73.94 (C-6, 2',3',5'), 71.42 (C-4'), 62.56 (C-6'), 60.22 (C-9), 48.43 (C-16), 44.09 (C-13), 42.84 (N-CH_3); 41.01 (C-14), 35.75 (C-15), 21.73 (C-10).

Deacetylation of **12**, as described for the preparation of **8**, gave amorphous **14** in virtually theoretical yield: cims, *m/z* 490 ([M + 1]$^+$), 507 ([M + NH_4]$^+$); ^{1}H nmr spectrum (CD_3OD-D_2O) δ 5.83 (d, 1 H, $J_{1,2}$ 5.13 Hz, H-1'), 1.74 (s, 3-H, CH_3, orthoester), signals of protons for the morphine moiety.

b) A solution of **5** (990 mg, 1.5 mmol), **2** (327 mg, 1 mmol) and 2,4,6-trimethylpyridine (200 µl, 1.5 mmol) in dichloromethane (5 ml) was added with stirring at -5 °C to a suspension of silver triflate (437 mg, 1.7 mmol) in dichloromethane (5 ml). After 15 min, tlc (solvent *C*) showed that all of **5** was consumed and that some unchanged **2** was still present. Three products were detected both by charring with sulfuric acid and by uv light, among which the one showing intermediate mobility was the minor product. The solution, which was neutral to litmus, was filtered through a Celite pad, washed with 10% aqueous sodium thiosulfate solution, dried, and concentrated. Chromatography gave slightly cross-contaminated (**13**, **15**, and **7**) in that order. Pure substances were obtained by rechromatography.

Orthobenzoyl derivative (**13**): amorphous, $[\alpha]_D$ -66.5° (c 0.7, chloroform); cims, *m/z* 906 ([M + 1]$^+$) and 923 ([M + 18]$^+$); ^{1}H nmr ($CDCl_3$) δ 6.23 (d, 1 H, $J_{1,2}$ 5.4 Hz, H-1'), 5.88 (t, 1 H, *J* 2.9 Hz, H-3'), 5.56-5.62 (m, 2 H, H-4, overlapped by a 1-proton signal of morphine), 5.12 (br t, 1 H, H-2'), 4.57 (dd, 1 H, $J_{5',6'a}$ 2.9 Hz, $J_{6'a,6'b}$ 12.2 Hz, H-6'a), 4.37 (dd, 1 H, $J_{5',6'b}$ 4.4 Hz, H-6'b), 4.18 (dbt, 1 H, H-5'); ^{13}C nmr spectrum ($CDCl_3$) showed signals characteristic[9] of the carbon atoms of the phenyl group attached to C-7', and of C-7' of orthobenzoates at δ 134.92, 126.77, and 121.47, respectively. In the range of 58-100 ppm there were present

six ^{13}C signals of the glucosyl residue and, as expected,[7] three of the ^{13}C signals of morphine: δ 98.21 (C-1'), 91.76, 72.63, 70.07, 68.90, 68.28, 67.84, 63.66 (C-6'), and 58.86. *Anal.* Calcd for $C_{53}H_{47}NO_{13}$: C, 70.26; H, 5.22; N, 1.54. Found: C, 70.06; H, 5.36; N, 1.45.

α-Glycoside (**15**): amorphous, $[\alpha]_D$ +24.5° (c 0.5, chloroform), cims, *m/z* 906 ($[M + 1]^+$) and 923 ($[M + NH_4]^+$); ^1H nmr ($CDCl_3$) δ 6.26 (t, 1 H, *J* 9.8 Hz, H-3'), 5.70 (t, 1 H, *J* 10 Hz, H-4'), 5.54 (d, 1 H, $J_{1',2'}$ 3.9 Hz, H-1'), 5.36 (dd, 1 H, H-2'), 5.02 (ddd, 1 H, $J_{5',6'a}$ 2 Hz, $J_{5',6'b}$ 5 Hz, H-5'), 4.74 (dd, 1 H, $J_{6'a,6'b}$ 12.3 Hz, H-6'a), 4.48 (dd, 1 H, H-6'b); ^{13}C nmr ($CDCl_3$) δ 98.18 (C-1'), 91.90 (C-5), 77.23 (C-6), 71.91 (C-2'), 70.62 (C-3'), 69.49 (C-4'), 68.70 (C-5'), 62.96 (C-6'). *Anal.* Calcd for $C_{53}H_{47}NO_{13}$: C, 70.26; H, 5.22; N, 1.54. Found: C, 70.06; H, 5.30; N, 1.48.

Deacylation of **15** as described for the preparation of **8**, except that the reaction was carried out at 60 °C, gave, after purification of the crude product by chromatography, **16** in a virtually theoretical yield. Crystallization from aqueous methanol afforded pure material (tlc, nmr) as a monohydrate; mp 175-177 °C; $[\alpha]_D$ -53° (c 1, water); cims, *m/z* 448 ($[M + 1]^+$) 465 ($[M + 18]^+$); eims *m/z* 447 ($[M]^+$); ^{13}C nmr (D_2O) δ 146.35 (C-4), 139.24 (C-3), 130.60 (C-12), 129.68, 128.92 (C-7,8), 125.44 (C-11), 119.98 (C-1), 117.58 (C-2), 98.72 (C-1'), 91.32 (C-5), 73.26, 73.07, 72.41, 71.52 (C-3',2',5',6), 69.87 (C-4'), 60.91 (C-6'), 58.46 (C-9), 45.82 (C-16), 43.44 (C-13), 41.48 ($N-CH_3$), 39.61 (C-14), 33.95 (C-15), 20.87 (C-10). *Anal.* Calcd for $C_{23}H_{29}NO_8 \cdot H_2O$: C, 59.34; H, 6.71; N, 3.00. Found: C, 59.68; H, 6.81; N, 3.02.

β-Glycoside (**7**): amorphous, $[\alpha]_D$ -58° (c 1, chloroform); cims, *m/z* 906 ($[M + 1]^+$); ^1H nmr ($CDCl_3$) δ 5.90 (t, 1 H, *J* 9.0 Hz, H-3'), 5.77-5.68 (m, 2 H, H-4', partially overlapped by a 1-proton signal of morphine), 6.60 (dd, 1 H, $J_{1',2'}$ 7.4 Hz, $J_{2',3'}$ 8.9 Hz, H-2'), 5.29-5.20 (m, 2 H, H-1', partially overlapped by a 1-proton signal of morphine), 4.66 (dd, 1-H, $J_{5',6'a}$ 3 Hz, $J_{6'a,6'b}$ 12 Hz, H-6'a), 4,53 (dd, 1 H, $J_{5',6'b}$ 5.6 Hz, H-6b), 4.27 (ddd, 1-H, $J_{4,5}$ 9.3 Hz, H-5'); ^{13}C nmr ($CDCl_3$): δ 99.29 (C-1'), 90.14 (C-5), 73.50, 73.09, 72.39, 72.14 (C-3',5',2',6), 69.69 (C-4'), 63.24 (C-6'), and the requisite signals of the morphine moiety. *Anal.* Calcd for $C_{53}H_{47}NO_{13}$: C, 70.26; H, 5.22; N, 1.54. Found: C, 70.20; H, 5.26; N, 1.56.

Deacylation of **7**, in the manner similar to that described above for the preparation of **12**, gave, after purification of the crude product by chromatography, material indistinguishable from **8** described earlier.

c) A solution of **5** (0.62 g, 0.95 mmol) and **2** (208 mg, 0.63 mmol) in dichloromethane (5 ml) was added with stirring at -5 °C to a suspension of silver triflate (0.26 g, 1.0 mmol) in dichloromethane (5 ml). After 15 min, tlc (solvent *C*) showed that all glycosyl donor was consumed and that only a trace of **2** remained. The same three products as in b) were detected by charring with sulfuric acid and by uv light, but only a trace of **13** was present.

The mixture was filtered, through a pad of Celite, into a separatory funnel containing a 1:1 mixture of 5% aqueous sodium thiosulfate and sodium hydrogen carbonate solutions. After conventional work-up, the crude product was chromatographed, to give **15** (114 mg, 20%) and **7** (440 mg, 76.6%).

6-*O*-β-D-Glucopyranosylcodeine (16). A solution of **3** (0.898 g, 3 mmol) and the glycosyl donor (**5**) (2.76 g, 4.0 mmol) in dichloromethane (10 ml) was added at -5 °C to a stirred suspension of silver triflate (1.15 g. 4.5 mmol) in dichloromethane (8 ml). When the addition was complete, the cooling was terminated and, when tlc (solvent *C* and *D*) showed that the reaction was complete, the mixture was worked-up as described for the preparation of **7** and **15** (c). The crude product was chromatographed first using a chloroform-methanol mixture as the eluant. The major zone was divided into several fractions each of which was then re-chromatographed using a mixture of ethyl acetate-methanol as the solvent. The material collected from the front of the uv positive zone (0.14 g, 5.3%) was a ~4:6 mixture of **9** and **15**, as shown by ^{1}H nmr spectroscopy. ^{1}H Nmr ($CDCl_3$) δ 6.25 (t, *J* 9.9 Hz, H-3), 5.77 (t, partially overlapped, *J* 10.1 Hz, H-4), 5.55 (d, $J_{1,2}$ 3.8 Hz, H-1), 5.34 (dd, overlapped, H-2), 5.20 (ddd, partially overlapped, H-5), 4.77 (dd, $J_{5,6a}$ 2.3 Hz, $J_{6a,6b}$ 12.6 Hz, H-6a), 4.54 (dd, overlapped, H-6b), and the signals for protons of the codeine moiety; ^{13}C nmr ($CDCl_3$) δ 98.23 (C-1), 70.81 (C-2), 69.91, (C-3) 69.34 (C-4), 68.60 (C-5), 63.19 (C-6).

The rest of the material contained only **9** (nmr), which solidified on standing in an open flask for several days. Crystallization from dichloromethane-ethanol gave 1.76 g (67%) of **9** as a hemihydrate. The material melted unsharply between 110-115 °C, and this situation remained essentially the same after recrystallization from the same solvent, $[\alpha]_D$ -100° (c 0.65, chloroform); cims, *m/z* 878 ($[M + 18]^+$); ^{1}H-nmr ($CDCl_3$) δ 5.95 (t, 1 H, *J* 9.6 Hz, H-3'), 5.69 (t, partially overlapped, *J* 9.6 Hz, H-4'), 5.62 (dd, 1 H, $J_{1,2}$ 7.6, $J_{2,3}$ 9 Hz, H-2'), 5.34 (d, 1 H, H-1'), 4.66 (dd, 1 H, $J_{5,6a}$ 3.2, $J_{6a,6b}$ 12.1 Hz, H-6'a), 4.54 (dd, 1 H, $J_{5,6b}$ 5.6 Hz, H-6'b), 4.27 (ddd, 1 H, H-5'); ^{13}C nmr ($CDCl_3$); δ 98.65 (C-1'), 73.16 (C-3'), 72.51, 72.42, 72.18 (C-2',5',6), 69.92 (C-4'), 63.27 (C-6').

The material that remained in the mother liquor was virtually pure **9** (0.26 g, 9.9%), as shown by tlc and nmr spectroscopy. *Anal.* Calcd for $C_{52}H_{47}NO_{12}\cdot 0.5\,H_2O$: C, 70.41; H, 5.68; N, 1.57. Found: C, 70.47; H, 5.59; N, 1.54.

Compound (**9**) was debenzoylated as described for **7**, and the crude product was chromatographed. A solution of the chromatographically pure material was added dropwise to hexane with stirring, and the white precipitate was collected to give **11** as an amorphous, hygroscopic solid in a virtually theoretical yield: $[\alpha]_D$ -190° (c 1, ethanol); ^{13}C nmr (CD_3OD) δ 148.29 (C-4), 143.53 (C-3), 132.51 (C-7), 131.76 (C-12), 129.09 (C-8), 128.16 (C-11),

120.66 (C-1), 114.75 (C-2), 103.50 (C-1'), 90.74 (C-5), 78.11, 77.82 (C-3',5'), 75.40, 74.25 (C-2',6), 71.55 (C-4'), 62.69 (C-6'), 60.36 (C-9), 57.14 (OCH_3), 48.53 (C-16), 44.14 (C-13), 42.91 (N-CH_3), 41.14 (C-14), 35.95 (C-15), 21.79 (C-10). *Anal.* Calcd for $C_{24}H_{31}NO_8$: C, 62.45, H, 6.77; N, 3.03. Found; C, 62.94; H, 6.71; N, 2.89.

6-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)codeine (18). a) A mixture of silver carbonate (4 g, 14.5 mmol), Drierite (2 g) and **3** (1 g, 3.3 mmol) was treated exactly as described by Casparis *et al.*[3] Tlc (solvent *A*) of the mixture which turned dark showed that approximately 50% of **3** had been converted into a faster moving product. The mixture was treated[3] with **4** and, when all of glycosyl donor was consumed, the mixture was worked up as described.[3] The crude product was chromatographed to give first **18** (723 mg, 34.8 %), mp 195-196 °C (from ethanol, twice) (lit.,[3] mp 196 °C, from ethanol). The nmr spectra of the material were identical with those described below in (b). Continued elution gave **19** (400 mg, 40%): mp 184-186 °C (from benzene), producing the characteristic red melt (lit.,[3] mp 181-182 °C, from benzene). An intermediate, mixed fraction was also obtained.

b) A solution of small amount of **8** in dry pyridine was treated at room temperature with excess of acetic anhydride for 5 h. Tlc (solvent *A*) then showed that the reaction was complete and that one product was formed. After conventional processing, the product (**18**) was crystallized from ethanol, mp 195-196 °C. ^{1}H Nmr ($CDCl_3$) δ 5.28 (t, partially overlapped, *J* 9.4 Hz, H-3), 5.15 (t, 1 H, *J* 9.8 Hz, H-4), 5.07 (dd, 1 H, $J_{1,2}$ 7.9 Hz, H-2), 4.92 (d, partially overlapped, H-1), 4.27 (d, partially overlapped, $J_{5,6a}$ 4.6, $J_{6a,6b}$ 12.5 Hz, H-6a), 4.18 (dd, 1 H, $J_{5,6b}$ 2.3 Hz, H-6b), 3.78 (m, overlapped, H-5), and signals of protons for codeine moiety; ^{13}C nmr ($CDCl_3$): δ 170.56, 170.19, 169.77, 169.41 (4 x CO), 147.54 (C-4), 142.11 (C-3), 130.69 (C-12), 130.42, 128.93 (C-7,8), 118.90 (C-1), 113.63 (C-2), 98.26 (C-1'), 88.46 (C-5), 72.93, 72.25, 71.94, 71.36 (C-2',3',5',6), 68.66 (C-4'), 62.03 (C-6'), 58.85 (C-9), 56.35 (OCH_3), 46.44 (C-16), 43.62 (C-13), 43.14 (N-CH_3), 41.24 (C-14), 36.17 (C-15), 20.72, 20.61, 20.50 (3 $COCH_3$, C-10). *Anal.* Calcd for $C_{32}H_{39}NO_{12}$: C, 61.03; H, 6.24; N, 2.22. Found: C, 60.72; H, 6.30; N, 2.18.

REFERENCES

1. H. Yoshimura, K. Oguri, and H. Tsukamoto, *Chem. Pharm. Bull.*; 1968, **16**, 2114.
2. P. Casparis, German Pat., No. 839799, Class 12p, Group 14, 1950, *Beilst*, Vol. **27**, 3rd and 4th Suppl., 2244.
3. P. Casparis, E. Kuhni, and E. Leinziger, *Pharm. Acta Helv.*, 1949, **24**, 145.

4. L. H. Welsh, *J. Org. Chem.,* 1954, **19**, 1409.

5. R. L. Lemieux, *Methods Carbohydr. Chem.,* 1963, **2**, 221.

6. B. Helferich and A. Berger, *Chem. Ber.,* 1957, **90**, 2492.

7. F. M. Kaspersen and C. A. A. van Boeckel, *Xenobiotica,* 1987, **17**, 1451.

8. F. I. Carroll, C. G. Moreland, G. A. Brine, and J. A. Kepler, *J. Org. Chem.,* 1976, **41**, 996.

9. P. Kováč and R. B. Taylor, *Carbohydr. Res.,* 1987, **167**, 153.

10. K. Bock and C. Pedersen, *Adv. Carbohydr. Chem. Biochem,* 1983, **41**, 27.

11. P. J. Garegg and T. Norberg, *Acta Chem. Scand.,* 1979, **B33**, 116.

12. R. K. Ness, H. G. Fletcher, and C. S. Hudson, *J. Amer. Chem. Soc.,* 1950, **72**, 2200.

13. J. Banoub and D. R. Bundle, *Can. J. Chem.,* 1979, **57**, 209.

14. P. Kováč and C. P. J. Glaudemans, *J. Carbohydr. Chem.,* 1988, **7**, 317.

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